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Epstein-Barr Virus-Associated Hemophagocytic Syndrome and Fatal Infectious Mononucleosis

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Virus-associated hemophagocytic syndrome (VAHS) has been thought to be a distinct clinical entity, characterized by intermittent fever, enlarged liver and spleen, and the appearance of hemophagocytosis. Hemopoietic cells are actively ingested by monocytes/macrophages in various organs, including lymph nodes, bone marrow, liver, and spleen. Epstein-Barr virus (EBV) is now thought to be one of the major causes for the development of this unique syndrome. Additionally, VAHS is often associated with fatal infectious mononucleosis (IM). The relationship between EBV-associated VAHS and fatal IM is discussed in this concise review. © 1996 Wiley-Liss, Inc.

Key words: Epstein-Barr virus, hemophagocytic syndrome, fatal infectious mononucleosis

INTRODUCTION

Hemophagocytic syndromes (HPS) may be divided into different clinical categories, consisting of 1) a sporadic disorder, 2) a form associated with acute infection, 3) a familial form seen in children, and 4) a form associated with malignant disorders, immunodeficiencies, or defective leukocyte function [1]. Histopathologically, lesions are characterized by a mononuclear cell infiltration with a prominent histiocytic proliferation and phagocytosis of blood cells.

Most patients with infection-related HPS are afflicted with viral infection, defining the so-called virus-associated hemophagocytic syndrome (VAHS) [2]. Some investigators have proposed that the clinical syndrome represents a direct response to a fulminant viral infection, whereas others propose that virus(es) triggers an uncontrolled histiocytic proliferation in individuals with an underlying cellular immunoregulatory imbalance. However, precise pathogenetic mechanisms are still undetermined. Recently patients with VAHS have been reported more frequently, and Epstein-Barr virus (EBV) infection is considered to be the cause of most cases. Generally, infectious mononucleosis (IM) is a benign, self-limiting disease associated with a primary EBV infection. However, rare cases develop severe or fatal IM; additionally, severe or fatal IM is commonly accompanied by VAHS [3]. These disorders are the subjects of this report.

HISTORY OF VIRUS-ASSOCIATED HEMOPHAGOCYTIC SYNDROME AND FATAL INFECTIOUS MONONUCLEOSIS

In the late 1970's, Risdall et al. [2] first reported 19 cases characterized by similar clinical symptoms and laboratory findings, consisting of intermittent fever, lymph-node enlargement, hepatosplenomegaly, a tendency to pancytopenia and a hemophagocytosis in various tissues, where hemopoietic cells were actively ingested by monocytes/macrophages. They named this disorder virus-associated hemophagocytic syndrome (VAHS), because most patients had a preceding virus-associated illness caused by herpes or adenoviruses. Additionally, spontaneous recovery was common in many cases. In the early 1980's, cases of VAHS associated with EBV infection were reported, some being fatal [4–6]. In these cases, the presence of IgM antibodies to viral capsid antigen (VCA) and the absence of IgG antibodies to EBV-determined nuclear antigen (EBNA) indicated primary EBV infection. Following these reports, there were additional reports of EBV-associated VAHS [7–11]. Initially, the outcome of

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EBV-associated VAHS was considered to be favorable. However, with more cases, the prognosis of EBV-associated VAHS was demonstrated to be poor. Some patients exhibited a rapidly deteriorating and fatal course, similar to the clinical course of patients with fatal IM [12,13].

Males with X-linked lymphoproliferative syndrome (XLP) often develop severe or fatal IM accompanied by HPS observed in affected tissues, such as lymph nodes, bone marrow, liver, and spleen [14,15]. Approximately 60% of patients with XLP manifest severe or fatal IM, with VAHS generally associated with primary EBV infection [16]. VAHS associated with XLP and VAHS without XLP are believed to be different clinical entities. However, some of the pathogenetic mechanism(s) may be similar [17]. The study of underlying pathogenetic mechanisms of XLP may clarify the relationship between VAHS and fatal IM.

IMMUNE EVENTS IN PATIENTS WITH EBV-ASSOCIATED VAHS AND FATAL IM

During the acute phase of IM, atypical lymphocytes in blood increase remarkably [18]. Enlarged lymph nodes contain infiltrating CD3-, CD4-, CD8-, CD20-, and NKH-1-positive cells [19]. In the course of the disease, EBV-specific cytotoxic T lymphocytes (CTL), mainly derived from CD8-positive cells, emerge and kill EBV-infected cells [18,20]. In contrast to the increased number of circulating CD8-positive cells, subsets of CD4-positive cells increase slightly, but are important for the immune events responsible for cell-mediated immunity or humoral immunity, since they produce interferon (IFN)-gamma or interleukin (IL)-4 [21]. Severely defective or imbalanced immune defenses against primary EBV infection often lead to fatal IM, primarily due to fulminant hepatitis and VAHS [22].

Recently, studies to ascertain the pathogenetic mechanism(s) of VAHS and fatal IM have focused on a possible imbalance of various cytokine networks [23]. We studied 5 patients with IM during the acute phase, and none showed increased serum levels of IFN-gamma or IFN-alpha [24]. A part of sera from 5 patients with fatal IM demonstrated increased levels of these IFNs. All of these patients succumbed to VAHS. This observation suggested that an imbalance of IFN production was associated with this complication. Markedly elevated levels of soluble IL-2 receptor were also noted in patients with VAHS [25]. Additionally, increased serum levels of IFN-gamma, macrophage-colony stimulating factor (MCSF), tumor necrosis factor (TNF)-alpha, and IL-6 were recently reported in patients with hemophagocytic lymphohistiocytosis [26]. MCSF is produced by T cells, and stimulates monocytes/macrophages. Furthermore, the major source of IL-6 and TNF-alpha is activated monocytes/macrophages. Therefore, an overproliferation of activated T

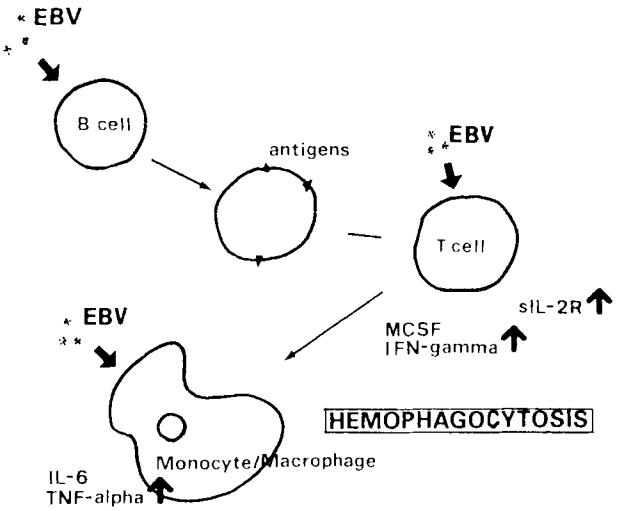

Fig. 1. Schematic hypotheses of immune events for Epstein-Barr virus (EBV)-associated hemophagocytic syndrome and fatal infectious mononucleosis (IM). EBV infects B cells, and/or T cells, and/or monocytes/macrophages, initially. Following these events, monocytes/macrophages are activated, and ingest various types of hemopoietic cells. Whether EBV directly infects T cells and/or monocytes/macrophages remains to be fully determined. In the case of virus-associated hemophagocytic syndrome or fatal IM, an overproliferation of activated T cells appears to play a significant role in the pathogenesis of the disease, because cytokines which were mainly produced by T cells were elevated in the circulation. sIL-2R, soluble interleukin-2 receptor; MCSF, macrophage-colony stimulating factor; IFN-gamma, interferon-gamma; IL-6, interleukin-6; TNF-alpha, tumor necrosis factor-alpha.

cells appears to be part of the syndrome of HPS, and the activation and/or overproliferation of T cells directed against EBV-infected cells may be a factor in HPS pathogenesis. Using molecular hybridization techniques, some have demonstrated T cells or monocytes/macrophages to be infected with EBV [27–29]. Therefore, EBV may infect T cells or monocytes/macrophages directly, and result in T cell or monocyte/macrophage proliferation. Additionally, NK cells contained EBV genome in one patient with VAHS [30], but these findings require confirmation. Though only B cells have been infected with EBV in healthy seropositive individuals [31], it is possible that other cells may be diseased in actively infected or immunocompromised individuals. Whether the immunophenotype of EBV-infected cells plays a major role in the pathogenesis of EBV-associated VAHS and fatal IM needs further study. Schematic hypotheses for the development of VAHS and fatal IM are shown in Figure 1.

In patients with primary or secondary immunodeficiencies, EBV-induced lymphoproliferative disorders (LPD) occur at an increased frequency [3]. Other than XLP, EBV-associated VAHS has rarely been documented in these patients, although non-EBV-associated VAHS

TABLE I. Therapeutic Approaches for Epstein-Barr Virus (EBV)-Associated Hemophagocytic Syndrome and Fatal Infectious Mononucleosis

Approach	Major target of action
1. Acyclovir	EBV
2. Ganciclovir	EBV
3. Adenine arabinoside	EBV
4. Immunoglobulins	EBV, B cell, T cell
5. Interferon-alpha	EBV, T cell, NK cell
6. Interferon-gamma	EBV, T cell, NK cell
7. Corticosteroids	Monocyte/macrophage, T cell, NK cell
8. Etoposide (VP16)	Monocyte/macrophage
9. Cyclosporine A	T cell
10. Anti-B-cell monoclonal antibodies	B cell
11. Bone marrow transplantation	Stem cell

occurs in patients with either primary or acquired immunodeficiencies. These LPD result from EBV-infected B-cell proliferations. Therefore, EBV-associated VAHS may occur in individuals who were previously immunocompetent. Though approximately 10% of patients with XLP have manifestations of XLP prior to EBV infection (e.g., lymphoma or dysgammaglobulinemia), the majority of patients have no evidence of immunodeficiency prior to EBV infection [16].

We recently described an unusual EBV infection in an XLP patient with fatal IM and VAHS [32]. A spontaneously-established cell line from an enlarged cervical lymph node demonstrated latent EBV infection in which no EBV replication occurred. In contrast, a combination of latent and lytic infection, in which EBV replication could occur, was noted in cell lines from blood lymphocytes. Latently infected cells may be less susceptible to lysis by natural killer (NK) cells and EBV-specific CTL. Restriction endonuclease enzyme-digested patterns of EBV were similar at each site, confirming one strain of virus, despite differing states of infection. These observations suggest that unknown defective controlling mechanisms for EBV infection exist at cellular levels in patients with severe EBV infection. Additionally, a variant EBV strain was isolated in 2 siblings with fatal lymphoproliferative disease [33]. This evidence indicated that a variant EBV strain might be responsible at least in part for the fatal course of these siblings, although further investigations are needed.

THERAPEUTIC APPROACHES FOR EBV-ASSOCIATED VAHS AND FATAL IM

Many therapies have been attempted against severe EBV infection [3]. These treatments include antiviral agents (such as acyclovir, ganciclovir, and adenine arabinoside), immunoglobulins, and immunomodulating agents such as IL-2, IFN-alpha, IFN-gamma, and corticosteroids. However, no beneficial effects have been clearly demonstrated from any of these treatments. Recently, etoposide was given to a patient with severe IM accompanied by VAHS who had XLP resulting in a clinical remission [34]. Etoposide mainly reduces the activity of monocytes/macrophages in vitro [35]. Although further clinical trials are necessary, Chinese investigators recently described an immunomodulatory regimen of intravenous immunoglobulins and/or etoposide that improved the prognosis of patients with HPS [36]. Additionally, cyclosporine A (CSA) or tacrolimus (formerly named FK506) may be useful in controlling the proliferation of T cells in spite of decreasing activity of EBV-specific CTL [3,37]. Of the over 150 affected males in the XLP registry (University of Nebraska Medical Center) who have had severe or fatal IM, there are 5 long-term survivors; 4 boys received etoposide and immunosuppressive therapies such as CSA (unpublished observations). Taken together, the current recommended approach for the treatment of VAHS or fatal IM is the use of etoposide with or without an immunomodulatory regimen. However, anti-B-cell monoclonal antibodies may be considered when infected B cells are thought to be a major factor in pathogenesis [38]. When underlying genetic factors for controlling EBV infection exist, such as XLP or familial HPS, intensive therapy supported by bone-marrow transplantation may be the treatment of choice [16,34]. Therapeutic approaches against EBV-associated VAHS and fatal IM, and a major target of action, are summarized in Table I.

CONCLUSIONS

In the 30 years since the discovery of EBV, this virus has been etiologically linked to a spectrum of human diseases. Previously unknown relationships may yet be detected by new diagnostic procedures. Furthermore, little is known about the pathogenetic mechanisms of EBV-associated diseases. Further advances in the recognition and differentiation of various EBV-associated entities should provide a more rational basis for the assessment of potentially effective therapies.

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